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Pharmacological agents to reduce readmissions in bipolar disorder

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Short title:

Prevention of hospitalisation in bipolar disorder

Abstract

It is well recognised that medications have an important role to play in preventing relapse in bipolar disorder. The impact these treatments have on rates of admission to hospital in particular has been less well studied. We combined data on hospitalisation from 11 randomised controlled trials in a network meta-analysis. We find that the published evidence demonstrates significant reductions in admission rates compared to placebo from lithium (RR 0.44, 95% CI 0.32 to 0.59), valproate (RR 0.50, 95% CI 0.28 to 0.90), the combination of lithium and valproate (RR 0.50, 95% CI 0.28 to 0.90), carbamazepine (RR 0.46, 95% CI 0.29 to 0.73), and olanzapine (RR 0.27, 95% CI 0.16 to 0.43). The evidence base contributing to these estimates remains fairly small, leading to broad confidence intervals for estimates of effect. More precise estimates could be obtained if unpublished outcomes data from other trials in this area became available. Several pharmacological treatments appear to be effective at reducing the need for hospital admission in people with bipolar disorder.

Keywords

Bipolar Disorder, Hospitalization, Antimanic Agents, Antipsychotic Agents, Meta-Analysis

Letter

It is well established that pharmacological treatments for bipolar disorder can prevent relapse (Goodwin et al., 2016). Strong evidence for this comes from over thirty randomised controlled trials. These data have been combined using conventional pair-wise meta-analysis (Beynon et al., 2009), and more recently through network meta-analysis (Miura et al., 2014), synthesising evidence from both direct and indirect treatment comparisons to generate best available estimates of effect.

While most treatment of bipolar disorder takes place in the community, for some people episodes of illness can lead to the need for admission to hospital. These admissions both act as a marker of serious relapse, associated with risks needing inpatient care, indicate inevitable social disruption, and also substantial economic impact. It has been estimated that the majority of healthcare costs attributed to bipolar disorder are due to hospitalisation (Young et al., 2011). The previous network meta-analysis (Miura et al., 2014) did not address the magnitude of effect on hospital admission rates of pharmacological treatment, although this is a clinically meaningful and pragmatic outcome measure for maintenance treatment. We sought to address this question from the available literature.

We identified 11 randomised controlled trials of pharmacological agents for the prevention of relapse in bipolar disorder that had published data on hospital admission rates by treatment allocation (Coxhead et al., 1992; Dunner et al., 1976; Esparon et al., 1986; Fieve et al., 1976; Geddes et al., 2010; Kleindienst and Greil, 2000; Lusznat et al., 1988; Prien, Caffey, et al., 1973; Prien, Klett, et al., 1973; Tohen et al., 2006, 2005). These studies compared eight treatment strategies. They are a subset of the 33 trials previously identified reporting effects on symptomatic

relapse (Miura et al., 2014). We combined these outcome data in a random effects network meta-analysis using R (version 3.2.4) with packages *meta* (version 4.4) and *netmeta* (version 0.9) (Rücker, 2012). Code available from the authors on request.

Figure 1 near here

We find that the published literature indicates significant reductions in admission rates compared to placebo from lithium (RR 0.44, 95% CI 0.32 to 0.59), valproate (RR 0.50, 95% CI 0.28 to 0.90), the combination of lithium and valproate (RR 0.50, 95% CI 0.28 to 0.90), carbamazepine (RR 0.46, 95% CI 0.29 to 0.73), and olanzapine (RR 0.27, 95% CI 0.16 to 0.43). Estimates were consistent with either harm or benefit for both imipramine (RR 1.13, 95% CI .51 to 2.50), and the combination of flupenthixol with lithium (RR 1.50, 95% CI 0.08 to 26.85).

The evidence base contributing to these estimates remains fairly small, leading to broad confidence intervals for estimates of effect, and new data could substantially affect these estimates. No hospitalisation data were available for other widely used treatments, such as quetiapine, which have been shown elsewhere to reduce relapse rates. Although it is unrealistic to expect many new trials of such treatments to be reported in the short term, improved estimates could be obtained if unpublished outcomes data from existing trials in this area were made available.

The estimates of effect may have been differentially affected by use of enrichment designs in some studies (Cipriani et al., 2013), and thresholds for hospital admission may well vary between settings depending on bed availability or provision of alternative crisis services. It will be important to consider these findings in the context of observational data (Joas et al., 2015); contrasts between experimental and observational data have been recently described for efficacy in prevention of relapse

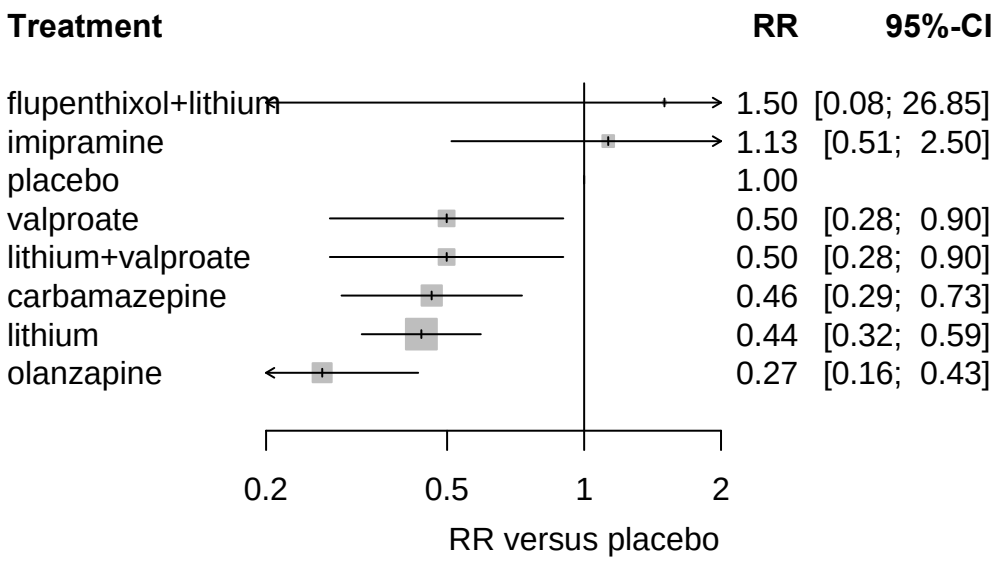
in bipolar disorder assessed by rates of monotherapy treatment failure (Hayes et al., 2016).

The reductions in rates of hospital admission from this analysis are fairly similar between most agents where data are available. This contrasts with relapse prevention efficacy for episodes of mania and depression where substantial differences in relative effects are seen, correlating with differences in efficacy in the treatment of acute episodes (Miura et al., 2014; Taylor, 2014). It is possible that the broad confidence intervals surrounding estimates for each agent may obscure underlying differences in effect that could emerge should further data become available.

Pharmacological treatments are not the sole approach likely to affect hospital admission rates. Group psychoeducation, for example, has a developing evidence base in relapse prevention for bipolar disorder (Bond and Anderson, 2015), and a specialist mood disorder clinic model combining medication management, following BAP prescribing guidelines (Goodwin et al., 2016), with a group programme achieved a substantial reduction in hospitalisation (Kessing et al., 2013). However, taken together, the published data from randomised controlled trials indicate that pharmacological agents can be an effective means of reducing need for hospital admission in people with bipolar disorder.

Legends

Figure 1. Best estimates for Relative Risk (RR) versus placebo for rates of hospital admission for pharmacological treatments for bipolar disorder. Random effects model; 95% Confidence Intervals (CI) shown.



Declaration of Interests

Dr. Taylor reports personal fees from Sunovion, Otsuka, Lundbeck, outside the submitted work, and a family member has been an employee of GlaxoSmithKline.

References

Beynon S, Soares-Weiser K, Woolacott N, et al. (2009) Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. *Journal of Psychopharmacology*, 23(5), 574–591.

Bond K and Anderson IM (2015) Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. *Bipolar Disorders*.

Cipriani A, Barbui C, Rendell J, et al. (2013) Clinical and regulatory implications of active run-in phases in long-term studies for bipolar disorder. *Acta Psychiatrica Scandinavica*.

Coxhead N, Silverstone T and Cookson J (1992) Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder. *Acta Psychiatrica Scandanavica*, 85(2), 114–118.

Dunner D, Stallone F and Fieve R (1976) Lithium carbonate and affective disorders V. A double blind study of lithium prophylaxis of depression in bipolar illness. *Archives of General Psychiatry*, 33(1), 117–120.

Esparon J, Kolloori J, Naylor GJ, et al. (1986) Comparison of the prophylactic action of flupenthixol with placebo in lithium treated manic-depressive patients. *British Journal of Psychiatry*, 148, 723–725.

Fieve R, Dunner D, Kumbaraci T, et al. (1976) Lithium carbonate prophylaxis of depression in three subtypes of primary affective disorder. *Pharmakopsychiatrie Neuropsychopharmakologie*, 9(3), 100–107.

Geddes JR, Goodwin GM, Rendell J, et al. (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet*, 375(9712), 385–395.

Goodwin GM, Haddad PM, Ferrier IN, et al. (2016) Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*.

Hayes JF, Marston L, Walters K, et al. (2016) Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. *World Psychiatry*, 15(1), 53–58.

Joas E, Karanti A, Lichtenstein P, et al. (2015) Effectiveness of Medication in Preventing Psychiatric Hospitalization in Bipolar Disorder - A Swedish Register-based Study. *Pharmacoepidemiology and drug safety*, 24(S1), 600.

Kessing LV, Hansen HV, Hvenegaard A, et al. (2013) Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *British Journal of Psychiatry*, 202(3), 212–219.

Kleindienst N and Greil W (2000) Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology*, 42 Suppl 1, 2–10.

Lusznat RM, Murphy DP and Nunn CM (1988) Carbamazepine vs lithium in the treatment and prophylaxis of mania. *British Journal of Psychiatry*, 153, 198–204.

Miura T, Noma H, Furukawa TA, et al. (2014) Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry*, 1(5), 351–359.

Prien RF, Klett CJ and Caffey EM Jr (1973) Lithium carbonate and imipramine in prevention of affective episodes. A comparison in recurrent affective illness. *Archives of General Psychiatry*, 29(3), 420–425.

Prien RF, Caffey EM Jr and Klett CJ (1973) Prophylactic efficacy of lithium carbonate in manic-depressive illness. Report of the Veterans Administration and National Institute of Mental Health collaborative study group. *Archives of General Psychiatry*, 28(3), 337–341.

Rücker G (2012) Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods*, 3(4), 312–324.

Taylor MJ (2014) Bipolar treatment efficacy. *Lancet Psychiatry*, 1(6), 418.

Tohen M, Greil W, Calabrese JR, et al. (2005) Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *American Journal of Psychiatry*, 162(7), 1281–1290.

Tohen M, Calabrese JR, Sachs GS, et al. (2006) Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *American Journal of Psychiatry*, 163(2), 247–256.

Young AH, Rigney U, Shaw S, et al. (2011) Annual cost of managing bipolar disorder to the UK healthcare system. *Journal of Affective Disorders*, 133(3), 450–456.